IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	10/567,899	Confirmation No.: 7174
Applicant(s):	Filho *et al.*	
Filed:	August 10, 2006	
Art Unit:	1755	
Examiner:	Mi, Qiuwen	
Title:	PHARMACEUTICAL COMPOSITION COMPRISING PLANT MATERIAL OR TRICHILIA SP. ALONE OR IN ASSOCIATION WITH OTHER PLANT EXTRACTS FOR THE REVERSION/COMBAT AND/OR PREVENTION OF VENTRICULAR FIBRILLATION	

Docket No.: 033794/307767
Customer No.: 00826

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RULE 37 C.F.R. §1.132 DECLARATION
of DR. IRINEU TADEU VELASCO

I, Dr. Irineu Tadeu Velasco, do hereby declare and say as follows:

1. I am skilled in the art of the field of the invention. I received a Ph.D. in Physiology and Pharmacology at Biomedical Sciences Institute of USP and obtained medical degree from Medical Sciences School of Santa Casa of São Paulo - FCMSCSP. I am currently a Professor of Clinical Medicine at the Medical School of the University of São Paulo (USP).

2. I have read and understood the Office Action in the above case dated May 23, 2008.

3. The Examiner alleges in the Office Action of May 23, 2008 that claims 1, 2, 6, 9-10, 15, 16, and 23-32 are obvious in view of the combination of Andre *et al.* (WO20029644l), Sander *et al.* (US 6,335,039), and Kowey *et al.* ((1982) *Cardiovascular Res.* 17:106-112). As presented below in Items 4, 5, 6, and 7, one of skill in the art would not have had a reasonable

expectation of success in the use of *Trichilia catigua* for the combat or reversion of ventricular fibrillation.

4. Myocardial ischemia is undoubtedly related to ventricular fibrillation (VF) and sudden cardiac death. It is widely known that patients with coronary heart disease have an increased risk of dying suddenly if not properly treated. It is also known that when myocardial ischemia is resolved, the risk for sudden death decreases significantly. This, however, does not imply that vasodilating the heart will solve the problem. We know that ischemia is the most potent vasodilator, and that giving vasodilating medication to a patient with critical coronary artery obstruction does not change mortality at all. In fact, vasodilators are used for coronary heart disease patient simply as a symptomatic medication (ISIS-4 Collaborative Group (1995) ISIS-4: A randomized factorial trial assessing early oral captoril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 345:669-685; Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (1994) GISSI-3: Effects of lisinopril and transdermal grlycery trinatrate singly and together on 6-week mortality and ventricular function after acute myocardil infartion. *Lancet*, 343:1115-1122).

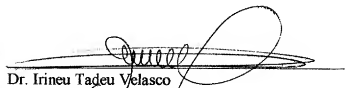
5. The Kowey *et al.* manuscript cited by the Examiner is an experimental study from the 1980's showing that coronary vasoconstriction (and consequently ischemia) induced by catecholamine decreased fibrillation threshold and consequently that vasodilators, in this setting, increase fibrillation threshold. This is absolutely true, but restrained to a specific situation and does not at all signalize the use of vasodilators for fibrillation prevention. There is a very interesting and broad review (Gheeraert *et al.* (2006) Risk factors for primary ventricular fibrillation during acute myocardial infarction: a systematic review and meta-analysis. *Eur. Heart J.*, 27:2499-2510) analyzing all the factors implicated in the risk of VF during acute myocardial infarction. Medications, and consequently the use of vasodilators, are not even cited.

6. The mechanism of VF, independently if related to ischemia or not, involve very complex electrophysiologic alterations (Weiss *et al.* (2004) *Ann. NY Academy of Sciences*, 1015:122-132) describe these mechanisms and interactions in details, and show that electrophysiologic, and mostly important, conduction and refractoriness alterations are very

important in the determination of VF. Thus, vasodilatation itself does not justify an antifibrillatory action.

7. Finally, I looked at the literature regarding VF from 2000 to now. I found 615 manuscripts, from which 615 were reviews. None of them take vasodilators into consideration in the treatment or prevention of VF. Thus, it is my conclusion that the Kowey *et al.* manuscript represents just an isolated observation and that, most important, it does not propose to treat or prevent VF with vasodilators, but just contributes to a better understanding of the mechanisms involved in sudden cardiac death.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



09/08/2008
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